Decision Memo for Venofer: Intravenous Iron Therapy (CAG-00080N)

Decision Summary

The *Coverage Issues Manual* will be revised to indicate that Medicare covers both sodium ferric gluconate complex in sucrose injection and iron sucrose injection when used as a first line treatment of iron deficiency anemia in patients undergoing chronic hemodialysis who are receiving supplemental EPO therapy.

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Decision Memo

TO: Administrative File: CAG–00080N
Venofer® (iron sucrose injection)
Intravenous iron replacement therapy for hemodialysis patients

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SUBJECT: National Coverage Decision
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This memorandum serves four purposes: (1) provides an overview of intravenous (IV) iron products; (2) reviews Medicare's coverage policy on IV iron therapy, and provides a timeline of recent activities; (3) presents and analyzes relevant scientific and clinical data related to iron sucrose; and (4) delineates the reasons for revising Medicare's national coverage policy on IV iron drugs to include iron sucrose.

IV Iron Supplementation

There are three different IV iron preparations currently available on the market for end-stage renal disease (ESRD) patients with iron deficiency anemia: (1) iron dextran, (2) sodium ferric gluconate, and (3) iron sucrose. IV iron preparations were first introduced to the United States market around 1991. Between 1991 and 1999, there were two IV iron products, both dextran-based, available for use (InFeD and DexFerrum). Both iron dextran products are indicated for use as a second-line therapy only after patients fail oral iron therapy. The Food and Drug Administration (FDA) considers iron dextran products as second line treatment options because they have demonstrated a small incidence (0.7%) of severe, life-threatening anaphylaxis which are not dose-related. Evidence suggests that the dextran component itself is what triggers the severe, life-threatening anaphylactic reactions often associated with IV iron dextran products.[1] Although many practitioners believe that IV iron is the optimal therapeutic modality in treating iron deficiency, they are often reluctant in prescribing iron dextran due to the unpredictable potential of life-threatening anaphylaxis, despite the recommendations of the National Kidney Foundation-Dialysis Outcomes Quality Initiative (NKF-DOQI), and a low incidence of adverse reactions.[2]

Despite the potential dangers of IV iron dextran, there are some populations for whom this form of IV iron treatment is preferable to other IV iron products. Unlike other IV iron preparations, iron dextran is a large and stable complex that can be administered to patients in large doses with low toxicity resulting from transient iron overload. The stability of the dextran complex allows total-dose infusions of more than one gram of iron in a single dialysis session. This aspect of IV iron dextran can be useful in hemodialysis patients who have fewer than three sessions per week or who are undergoing home dialysis.

FDA Approval

On February 18, 1999, the FDA approved Ferrlecit® (sodium ferric gluconate complex in sucrose injection), a gluconate-based IV iron product, for "the treatment of iron deficiency anemia in patients undergoing chronic hemodialysis who are receiving supplemental erythropoietin (EPO) therapy."[3] No limitations were placed on its use as either a first or second line therapy option. Sodium ferric gluconate contains no dextran polysaccharides and can thus serve as an alternative to patients who exhibit dextran sensitivity. Due to its FDA indications, this product is also considered an alternative to oral iron therapy as a first line therapy option.

On November 6, 2000, the FDA approved Venofer® (iron sucrose injection), a sucrose-based IV iron product that has been used in Europe for nearly 50 years that is currently approved for marketing in over 40 countries. Iron sucrose, also known as iron saccharate, contains no dextran polysaccharides and, like sodium ferric gluconate, is indicated for "the treatment of iron deficiency anemia in patients undergoing chronic hemodialysis who are receiving supplemental EPO therapy." No limitations were placed on its use as either a first or second line therapy option. The FDA based its approval of Venofer on three studies: Charytan, *et al*. (2001), Van Wyck, *et al*. (2000), and one currently unpublished study.

History of Medicare's Coverage of IV Iron Therapy and Timeline of Recent Activities

In August 1999, The Health Care Financing Administration (HCFA) received a formal coverage request for sodium ferric gluconate from Schein Pharmaceutical, Inc., the makers of Ferrlecit®. On April 20, 2000, based on its analysis of the available scientific and clinical literature, HCFA issued a positive national coverage decision (NCD) for sodium ferric gluconate when used as a first-line treatment for iron deficiency anemia in patients undergoing chronic hemodialysis who are receiving supplemental EPO therapy.[4] As part of its review, the agency analyzed the extensive body of scientific literature available on iron deficiency in anemic ESRD patients and the importance of IV iron in the clinical management of these patients. HCFA concluded that the clinical evidence on IV iron therapy pointed to a significant benefit in the treatment of iron deficiency and anemia in Medicare's ESRD population, and therefore, the overall clinical management of these patients.

Since Venofer ® had not yet been approved by the FDA, the NCD could not apply to Venofer® or any other iron sucrose preparation. FDA approval is a prerequisite for a coverage consideration. On November 13, 2000, American Regent Laboratories, Inc., the makers of Venofer®, submitted a formal request for coverage of iron sucrose in the treatment of iron deficiency upon receiving FDA approval.

Summary of Evidence

Medical Literature

During its review of sodium ferric gluconate between August 1999 and April 2000, HCFA conducted a thorough analysis of the available literature on IV iron therapy in patients with ESRD. The evidence reviewed indicated that the mode of IV administration is perhaps the most effective method for treating for iron deficiency anemia in hemodialysis patients. Unlike oral iron products which must be absorbed through the gastrointestinal (GI) tract, IV iron products can be infused directly into the bloodstream in a form that is readily available to the bone marrow for red blood cell synthesis, resulting in an earlier correction of iron deficiency and anemia. The available evidence also suggested that there is almost no distinction between the various IV iron products in terms of effectiveness. Rather, a particular drug's safety profile, as determined by the FDA, is the true distinguishing factor among these iron therapies.

As part of this coverage review, HCFA analyzed twelve studies published on iron sucrose. Most were either cohort studies or case series, with a total of 826 patients. No randomized clinical trials were conducted on iron sucrose. Specific information on each study can be found in Appendix B. The six studies summarized below provide the strongest evidence regarding the effectiveness of iron sucrose.

As part of its review for market approval, the FDA analyzed data provided in Charytan, *et al.* (2001), an open-label, single-arm, prospective multi-center study. Researchers examined the safety and effectiveness of iron sucrose therapy in 77 hemodialysis patients undergoing EPO therapy who were considered to be iron-deficient. Patients were administered a single dose of 100 mg of elemental iron over 10 consecutive dialysis sessions for a total of 1,000 mg of elemental iron over 22 days. The study's primary outcome measure was the percentage of patients who reached the target hemoglobin level range of 11.0 g/dL. At the 57-day follow-up, 66% of patients achieved the target hemoglobin level. Secondary outcome measures at day 57, including mean hemoglobin and serum ferritin levels, experienced significant increases compared to baseline. A significant increase in mean hemoglobin levels was first noted eight days (three doses) after the initial treatment dose. A total of 757 doses of iron sucrose were administered during the study. There were no serious adverse drug reactions recorded, no episodes of anaphylaxis, and no patient withdrawals or drug discontinuation caused by drug-related adverse events. The study demonstrates the effectiveness of iron sucrose in treating iron deficiency anemia in hemodialysis patients on EPO. Results from the study indicate that an initial correction of anemia may occur after only three doses (100 mg each) of iron sucrose.

Researchers in Van Wyck, *et al.* (2000), another open-label, single-arm, prospective study reviewed by the FDA, examined the safety and efficacy of iron sucrose therapy in 23 hemodialysis patients with documented sensitivity to iron dextran, ongoing EPO therapy, and below-target-range hemoglobin levels (< 11.0 g/dL). Patients were administered a single dose of 100 mg of elemental iron over 10 consecutive dialysis sessions for a total of 1000 mg of elemental iron over 22 days. The study's primary outcome measure was an increase in hemoglobin levels greater than 0.5 g/dL. A total of 223 doses of iron sucrose were administered during the study. There were no serious adverse reactions recorded, no episodes of anaphylaxis, no patient withdrawal, and no drug discontinuation caused by drug-related adverse events. Three mild adverse events possibly related to iron sucrose treatment were observed in two patients. All efficacy outcome measures showed a significant degree of improvement after therapy. Mean hemoglobin levels significantly increased from 10.4 g/dL at baseline to 11.5 g/dL at day 24 ($p<0.05$). Increases in hemoglobin levels first became significant at day 15 after six doses (600 mg) of iron sucrose. Mean serum ferritin levels significantly increased from 57.7 ng/mL at baseline to 324.0 at day 24 ($p<0.05$). EPO doses were stable prior to study and declined slightly during the study, a change that was not significant. This study demonstrates the safety and efficacy of iron sucrose as an alternative treatment in hemodialysis patients who have experienced adverse reactions to prior treatments of iron dextran.

The FDA also reviewed one currently unpublished study as part of its review of iron sucrose. This open-label, single arm, multi-center study conducted in South Africa examined the safety and efficacy of iron sucrose in 131 hemodialysis patients with dialysis-associated anemia, hemoglobin levels less than 100 g/L, serum transferrin saturation levels less than 20%, and serum ferritin levels less than or equal to 200 µg/L. Initially, a first dose of iron sucrose was given (50 mg of elemental iron) during the first hemodialysis session. This was followed by doses of 100 mg of elemental iron each administered during subsequent hemodialysis sessions. One hundred and five patients were included in the analysis of efficacy. Mean hemoglobin levels increased by 28% ($p < 0.0001$) at the end of the treatment period (week 2 of the observation period), and remained constant through final week of study (week 4 of the observation period). Mean serum ferritin levels were six to seven-fold higher at week 2 and at the final evaluation compared to baseline ($p < 0.0001$). All 131 patients were included in the safety analysis. The most frequently reported adverse events during the treatment period were hypotension (47%), cramps (37%), and nausea (24%), irrespective of the relationship to the study drug. Of those, events that were reported to be at least possibly related to the study drug by the treating clinician were hypotension (13%), cramps (1%), and nausea (3%). These adverse events were also associated with hemodialysis itself, and occurred with similar frequency during the subsequent observation period where no iron was given.

Hussain, *et al.* (1998) conducted a non-randomized, clinical trial that looked at the safety and effectiveness of iron sucrose and its comparability to oral iron therapy after three months of treatment. Twenty patients with hemoglobin levels less than 8.5 g/dL undergoing hemodialysis were enrolled and divided into two treatment groups. There was no description as to how these patients were divided. In Group 1 (n=10), patients were given iron sucrose and EPO. In Group 2 (n=10), patients were given oral ferrous sulfate and EPO. EPO doses in both groups were maintained for four weeks until hemoglobin levels rose to 11-12 g/dL. If levels exceeded this target, EPO doses were reduced by one half; EPO doses were doubled if target hemoglobin levels were not reached. At the end of the study, the iron sucrose group showed a significant increase ($p<0.001$) in hemoglobin levels compared to baseline (7.8 ± 0.24 to 11.6 ± 0.64 g/dl). Nine out of ten patients achieved the target hemoglobin levels. Mean serum ferritin levels also significantly increased ($p<0.05$) compared to baseline (386 ± 220 to 671 ± 388 ng/ml). Mean EPO doses at the end of three months in the iron sucrose group were 3400 ± 1356 units/week. In the oral iron group, hemoglobin levels significantly increased ($p<0.001$) compared to baseline (8.0 ± 0.44 to 10.5 ± 1.14 g/dl). Five out of ten patients achieved the target hemoglobin levels. Mean serum ferritin levels decreased slightly compared to baseline (446 ± 264 to 367 ± 238 ng/ml) but these results were not significant ($p=0.50$). Mean EPO doses at the end of three months in the oral iron group were 4600 ± 1356 units/week. Despite higher doses of EPO, few patients in Group 2 reached the target hemoglobin levels. The slight decrease in serum ferritin levels may indicate that the patient's iron needs still exceed iron intake. A greater percentage of Group 1 patients reached target hemoglobin levels despite receiving less EPO. The significant increase in serum ferritin levels may indicate that the intake of iron is both meeting the patient's iron needs and replenishing body iron stores.

Another non-randomized clinical trial, conducted by Silverberg, *et al.* (1996), examined the long-term effectiveness of iron sucrose in dialysis patients. A total of 73 patients on chronic dialysis participated in the study (64 were on hemodialysis and 9 were on continuous ambulatory peritoneal dialysis [CAPD]). Patients were stratified into five groups. Group 1 (n=41) consisted of those patients on hemodialysis who had been receiving EPO for at least six months. These patients began a regimen of iron sucrose twice monthly for one year. EPO doses were kept constant for the first six months after which doses were adjusted according to hematocrit levels. Group 2 (n=11) consisted of hemodialysis patients who previously never used EPO. These patients initiated EPO and iron sucrose therapy simultaneously for one year. EPO doses were adjusted according to hematocrit levels. Group 3 (n=12) hemodialysis patients also never received EPO. These patients initiated only iron sucrose therapy for one year. Group 4 (n=4) patients consisted of those CAPD patients who had been receiving EPO for at least six months. These patients also began a regimen of iron sucrose for six months. EPO doses were kept constant. Group 5 (n=5) consisted of CAPD patients who never received EPO. These patients began iron sucrose therapy. Results are shown in Table 1.

Table 1: Results of Iron Sucrose Therapy by Group

Group		EPO doses (IU/kg/week)	Hematocrit %	Serum Ferritin :g/L
HD on EPO starting IS (n=41)	baseline	98.8 ± 27.7	28.7 ± 1.5	99.0 ± 68.9
	12 mo.	38.4 ± 31.1*	33.6 ± 2.0*	383.3 ± 97.7*
HD starting IS and EPO (n=11)	baseline	0	28.1 ± 1.4	83.7 ± 48.5
	12 mo.	23.2 ± 16.3	33.9 ± 2.4*	348.8 ± 104.6*
HD starting IS (n=12)	baseline	0	30.5 ± 1.7	49.0 ± 29.0
	12 mo.	0	37.9 ± 3.9*	287.8 ± 147.2*
CAPD on EPO starting IS (n=4)	baseline	61.4 ± 16.6	28.4 ± 1.0	102.8 ± 54.0
	6 mo.	61.4 ± 16.6	33.3 ± 2.2*	470.5 ± 252.0*

Group		EPO doses (IU/kg/week)	Hematocrit %	Serum Ferritin :g/L
CAPD starting IS (n=5)	baseline	0	27.7 ± 1.7	144.6 ± 53.4
	6 mo.	0	35.6 ± 2.4*	459.9 ± 93.0*

HD = hemodialysis patients, IS = iron sucrose, CAPD = CAPD patients; *p < 0.05 vs. baseline

All five treatment groups experienced a significant improvement in hematocrit and serum ferritin levels at six and twelve month follow-ups. Group 1 (hemodialysis patients on EPO starting IV iron sucrose therapy) also experienced a significant reduction in weekly EPO dose requirements. It is interesting to note that even hemodialysis and CAPD patients who were treated with only iron sucrose experienced a statistically significant increase in hematocrit levels.

Researchers in Macdougall, *et al.* (1999) conducted an observational study on 116 hemodialysis patients receiving treatment in a dialysis facility. The main objective of the study was to determine the effect of IV iron therapy on EPO dose requirements. All patients were administered iron sucrose and followed for one year. Treatment was only withheld if serum ferritin levels exceeded 1000 : g/L. The main therapeutic goal was to keep hemoglobin levels between 10 and 12 g/dL. EPO doses were adjusted accordingly to reach and maintain this target value. At the end of the study, after one year, hemoglobin levels increased significantly ($p<0.005$) compared to baseline (9.6 ± 2.0 to 10.7 ± 1.9 g/dL). The percentage of patients with hemoglobin levels greater then 10 g/dL also increased from 41% at baseline to 68% after one year of treatment. Serum ferritin levels also showed a significant increase ($p<0.0001$) compared to baseline (214 ± 246 to 564 ± 350 : g/L). Mean EPO doses significantly decreased ($p<0.0005$) from 13,277 ± 6,330 to 8,976 ± 6,158 units per week. In total, 4,564 injections of iron sucrose were given to the study population. No adverse reactions were observed. This study supports the notion that the observed benefit of iron sucrose demonstrated in clinical trials can be reproduced when used outside the research setting.

The findings reported in the three studies mentioned above are consistent with the remaining nine studies also reviewed. Most patients improved after being treated with iron sucrose and no serious adverse reactions were reported in studies that were compiling safety data. However, the trials themselves have a number of design flaws that may affect the validity of their results. Most studies do not compare iron sucrose to a control group. Studies that had control groups did not randomize patients between treatment arms, failing to minimize the effects of selection bias on study results. This said, HCFA believes that the scientific evidence on iron sucrose is adequate to determine its effectiveness. Despite potential design flaws, the evidence is fairly consistent between studies and with standard medical theories, pointing to a benefit of iron sucrose in the treatment of iron deficiency anemia in patients with ESRD.

Practice Guidelines: NKF-DOQI

In March of 1995, the NKF-DOQI was established with the primary objective of improving patient outcomes and survival by recommending optimal clinical practices through the development of evidence-based practice guidelines. One of the clinical areas the DOQI workgroups focused on was anemia management and the role of iron supplementation. The following five issues were raised by the Anemia Work Group:

1. Iron (blood) losses are high, particularly in the hemodialysis patient.
2. Oral iron usually cannot maintain adequate iron stores, particularly in the hemodialysis patient treated with EPO.
3. EPO, by stimulating erythropoiesis to greater than normal levels, often leads to functional iron deficiency.
4. Prevention of functional (and absolute) iron deficiency by regular use of IV iron (i.e., small doses, weekly, to replace predicted blood losses) improves erythropoiesis.
5. The serum iron, total iron binding capacity, and serum ferritin are the best indicators of iron available for erythropoiesis and iron stores, but do not provide absolute criteria of either iron deficiency or iron overload.

A review of the medical evidence pointed to the inadequacy of oral supplementation in maintaining adequate body iron stores. The Anemia Work Group acknowledged that, although there may be some temporary improvements in hematocrit and hemoglobin levels with oral iron therapy, the rate of iron loss greatly exceeds the rate of GI absorption and, ultimately, body iron stores will become depleted. Most ESRD patients will eventually need IV iron treatment to replenish body iron stores. The evidence on IV iron has shown significant improvements in EPO response, as well as hemoglobin and hematocrit levels. A number of studies also point to significant reductions in the amount of EPO required to maintain adequate hemoglobin and hematocrit levels in patients undergoing IV iron therapy. After careful review of the clinical evidence, the Anemia Work Group recommended regular amounts of IV iron therapy in patients receiving EPO based on the following rationale:

1. Erythropoiesis requires both iron and EPO.
2. Oral iron fails to maintain adequate iron stores in most hemodialysis patients, resulting in persistence of moderate anemia, which increases morbidity and mortality.
3. The use of IV iron will increase hematocrit and hemoglobin levels, and therefore improve morbidity and survival in chronic renal failure patients.
4. The health benefits of IV iron are expected to exceed its adverse effects resulting in a net health benefit

HCFA Analysis

In addressing the potential for a national coverage policy on iron sucrose in the treatment of iron deficiency anemia in patients on chronic hemodialysis on EPO, the following questions arise:

- Is the evidence on iron sucrose adequate to determine its effectiveness in the treatment of iron deficiency in ESRD patients?
- Does the evidence suggest that the effectiveness of iron sucrose is equivalent to or better than oral iron therapy?
- Does the evidence suggest that the safety profile of iron sucrose is equivalent to or better than IV iron dextran?

Is the evidence on iron sucrose adequate to determine its effectiveness in the treatment of iron deficiency in ESRD patients?

There are no randomized clinical trials that demonstrate the effectiveness of iron sucrose in treating iron deficiency in patients with ESRD. The available evidence on iron sucrose has largely been developed through non-randomized cohort studies and case series. As summarized earlier, Hussain, *et al.* (1998), Silverberg, *et al.* (1996), and Macdougall, *et al.* (1999) all showed significant improvements in hemoglobin and/or hematocrit levels after being treated with iron sucrose. No serious adverse reactions were reported in Macdougall, *et al.* (1999) in which the study population was given 4,564 injections of iron sucrose. Most patients improved after being treated with iron sucrose and no serious adverse reactions were reported in studies that were compiling safety. Despite some study design flaws, the evidence is fairly consistent between studies, pointing to a benefit of iron sucrose in the treatment of iron deficiency anemia in patients with ESRD. In addition, high quality, evidence-based clinical practice guidelines support effectiveness.

Does the evidence suggest that the effectiveness of iron sucrose is equivalent to or better than oral iron therapy?

In order to answer this question, one must look at studies that compared oral iron therapy to iron sucrose therapy. The only study that compared these two methods of iron supplementation was reported in Hussain, *et al.* (1998). As mentioned earlier, Hussain, *et al.* (1998) found that both the oral and iron sucrose treatment groups had significant increased in hemoglobin levels. The iron sucrose group also showed a significant increase in serum ferritin levels, a measure of body iron stores. The oral iron group did not experience a significant improvement in body iron stores and even showed a slight decrease in serum ferritin levels. This study, however, did not randomize patients to a treatment group. The authors did not mention how patients were assigned to a particular treatment group. In addition, there is no way to determine whether the results of the study are consistent with other clinical trials since this is the only study that examined oral iron therapy versus iron sucrose.

Other studies have been conducted that examine the comparative effectiveness of IV iron therapy to oral iron therapy, many of which were examined in the analysis on sodium ferric gluconate. Although these studies used IV iron products other than iron sucrose, these types of trials are relevant given that the available medical literature suggests there is little to distinguish various forms of IV iron therapy in terms of effectiveness. The true distinction among IV iron products lies within their safety profiles.

Does the evidence suggest that the safety profile of iron sucrose is equivalent or better than IV iron dextran?

No randomized clinical trials have been conducted to measure the comparative effectiveness of IV iron dextran, sodium ferric gluconate, and iron sucrose. However, the evidence suggests that these drugs would not differ on effectiveness, but rather safety.[5, 6] All three IV iron products have a certain degree of risk associated with their use in ESRD patients. Yet, the FDA felt that the safety data available on these three iron products warranted differential labeling. The FDA restricted use of both IV iron dextran products to patients "with documented iron deficiency in whom oral administration is unsatisfactory or impossible" due to the "anaphylaxis and other hypersensitivity reactions [that] have been reported after uneventful test doses as well as therapeutic doses."[7] This indication requires ESRD patients to undergo an initial regimen of oral iron despite evidence demonstrating its low effectiveness in the treatment of iron deficiency anemia. The labeled indications for the two non-dextran based IV iron products are not as stringent based on the lack of observed anaphylactic reactions. Due to their less restrictive labeling, both sodium ferric gluconate and iron sucrose can be considered alternatives to IV iron dextran *and* oral iron therapy. Patients can initiate treatment with these IV iron therapies without a prior course of oral iron.

In HCFA's analysis on sodium ferric gluconate, the available evidence suggested that the administration of this drug has not resulted in life-threatening anaphylaxis similar to those reactions found in IV iron dextran products. The evidence also demonstrated that IV administration of supplemental iron is a more effective therapy for iron deficiency (both functional and absolute) in hemodialysis patients compared to oral iron therapy. In April 2000, HCFA concluded a national policy was warranted in covering sodium ferric gluconate for the first line treatment of iron deficiency anemia in patients undergoing chronic hemodialysis and receiving supplemental EPO therapy.

The evidence reviewed on iron sucrose also supports the use of this IV iron product as an alternative to IV iron dextran and oral iron therapy. The body of evidence on iron sucrose, as well as its use in clinical practice for over 50 years throughout Europe, suggests that administration of iron sucrose is not associated with life-threatening anaphylaxis. Given that its FDA-approved indication is the same as the indication for sodium ferric gluconate and the evidence that suggests that IV iron supplementation plays a prominent role in the clinical management of iron deficiency anemia in ESRD patients, a national policy covering iron sucrose is warranted. Therefore, HCFA will revise its current national policy on IV iron therapy to also include coverage of iron sucrose in the first line treatment of iron deficiency anemia in patients undergoing chronic hemodialysis who are receiving supplemental EPO therapy. This revision in Medicare's national coverage policy will result in identical policies for sodium ferric gluconate and iron sucrose, thereby maximizing patient and physician choice.

Decision

The *Coverage Issues Manual* will be revised to indicate that Medicare covers both sodium ferric gluconate complex in sucrose injection and iron sucrose injection when used as a first line treatment of iron deficiency anemia in patients undergoing chronic hemodialysis who are receiving supplemental EPO therapy.

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1 Faich G, et al. 1999.

2 Frankenfield D, et al. 2000.

3 FDA labeling for Ferrlecit®.

4 Decision Memorandum CAG-00046 on sodium ferric gluconate.

5 Bailie G, et al. 2000.

6 Sunder-Plassmann G, et al. 1999.

7 FDA labeling for INFeD®.

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